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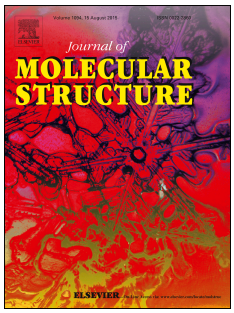

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Synthesis, Crystal Structure, and Non-Covalent Interactions in Ethyl 4-Hydrazinobenzoate Hydrochloride.

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ABSTRACT

The compound ethyl 4-hydrazinobenzoate hydrochloride (E-4HB), $C_9H_{13}N_2O_2Cl$, has been synthesized and characterized by FT-IR, ^1H and ^{13}C NMR and X-ray diffraction. The compound crystallizes as colourless plates in the triclinic space group *P*-1, with Z' = 2 and cell parameters a = 5.9566 (4) Å, b = 7.4498 (6) Å, c = 23.5349 (17) Å, α = 84.323 (3), β = 84.521 (3), γ = 80.257 (3), V = 1020.95 (13) Å^3. The component ions are linked by two N-H...N hydrogen bonds and eight N-H...Cl hydrogen bonds to form complex sheets in which each of the chloride ions accepts hydrogen bonds from four different cations. Calculations on the Non-Covalent Interactions (NCI) amplify the crystallographic conclusions concerning the intermolecular hydrogen bonds.

Keywords: synthesis, crystal structure, molecular structure, hydrogen bonding, modelling of non-covalent interactions.

1. INTRODUCTION

Phenylhydrazines are highly reactive reagents commonly employed in identifying and purifying aldehydes and ketones, particularly sugars. They are also very useful precursors for the synthesis of dyes, pharmaceuticals and other organic intermediates [1,2]. Phenylhydrazine derivatives have also been used in the treatment of *polycythaemia vera*, a condition involving over-production of red blood cells which, if untreated, often proves fatal [3].

Compounds of this general type are useful as intermediates for the synthesis of novel heterocyclic and hydrazone compounds [4–7], and we have been interested in the synthesis of new phenylhydrazone derivatives because of their broad spectrum of biological activity, including anti-inflammatory, antimalarial, antitumor, and antiviral activity, as well as acting as analgesics and vasodilators [8,9]. To this end, we have recently used the compound E-4HB to synthesize new furan-2- and thiophen-2-phenylhydrazone derivatives [6], in order to assess their interactions with human serum albumin, (target biomolecule for cancer treatment), using both spectroscopic and molecular docking techniques [10–14].

In addition, the chemical and physical properties of these compounds, such as thermal stability, high crystallinity, chemical inertness and π conjugation make compounds of this type suitable for nonlinear optical applications [7], and the richness of non-covalent interactions arising from the hydrazone unit has led to their proposed use as sensors for a range of anions such as fluoride and acetate [9].

Despite the wide range of applications, both confirmed and potential, there are only a few structural reports on salts of this type [15–17], and we discuss this briefly in Section

3.2.1 below. Here we report the molecular and supramolecular structure of the compound E-4HB, together with a computational study of the non-covalent interactions present in the crystal structure. The compound was synthesized using the reductive diazotization of ethyl 4-aminobenzoate (benzocaine 1) (Scheme 1) [18,19].

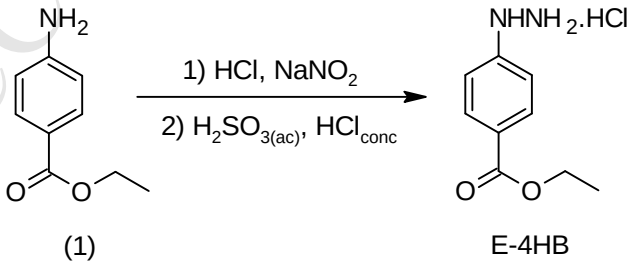
2. EXPERIMENTAL

2.1. General procedure and materials

Melting points were determined on a digital IA-9100 ELECTROTHERMAL Fusiometer. IR spectra were recorded on a Shimadzu Model IR Prestige21 FT-IR Spectrometer in KBr pellets. NMR spectra were measured using a "Brukerbiospin 500" (500 MHz for ^{1}H and 125 MHz for ^{13}C). X-ray diffraction data were collected using a *KAPPA* DUO PAEXII diffractometer.

2.2. Synthesis of ethyl 4-hydrazinobenzoate hydrochloride (E-4HB).

The synthesis at the compound E-4HB comprises two steps: the first is the preparation of a diazonium salt and the second is the reduction of this salt with a saturated aqueous solution of sulfur dioxide to form the corresponding hydrazine hydrochloride (Scheme 1) [18,19].



Scheme 1. Synthesis of E-4HB.[18–20].

2.2.1. Preparation of the diazonium salt from ethyl 4-aminobenzoate (1).

In a 100 mL round bottom flask provided with a magnetic stirrer and cooled in an ice-

salt bath were placed 7.5 mmol of the ethyl 4-aminobenzoate (1) suspended in 7 mL of distilled H_2O with continuous stirring. Then, 8.1 mL of concentrated aqueous hydrochloric acid (37 %) were added. After the mixture had been cooled to 0 ºC, a solution of sodium nitrite (7.5 mmol in 5 mL of distilled water) was added dropwise over a period of 30 minutes and then the stirring was continued for 15 minutes more. The clear orange diazonium salt solution was then diluted with 15 mL of distilled water [18,19].

2.2.2. Reduction of the diazonium salt with aqueous sulfur dioxide.

In a 500 mL round bottom flask, surrounded by an ice-salt bath, 60 mL of distilled water was saturated with a stream of gaseous sulfur dioxide at 0-5 ºC. The stream of the gas was continued while the cold diazonium salt solution was added in 3 mL aliquots at intervals of 15 minutes, awhile maintaining the temperature between 5 and 10 ºC. The reaction mixture became dark, and then sulfur dioxide gas was passed into the mixture for a further 20 minutes without the cooling bath. Finally, 71 mL of concentrated aqueous hydrochloric acid was added and the mixture was chilled to 0-5 ºC for 12 hours.

The product E-4HB was collected by filtration, and washed with two portions of 10 mL of cold concentrated aqueous hydrochloric acid [18,19]. The compound E-4HB was recrystallized from a mixture of 10 mL distilled water and 1 mL concentrated hydrochloric acid, the solution was boiled briefly with activated charcoal, and after removal of the charcoal by filtration, 1 mL of concentrated aqueous hydrochloric acid was added [18]. The whole mixture was cooled to 0 ºC, and compound E-4HB was collected by filtration, in the form of colourless plates suitable for single-crystal X-ray diffraction.

2.3. Refinement

Crystal data, data collection and structure refinement details are summarized in Table 1: standard software was sued throughout [21–23]. All H atoms were located in difference maps. The H atoms bonded to C atoms were then treated as riding atoms in geometrically idealized positions with C-H distances 0.95 Å (aromatic), 0.98 Å (-CH_3) or 0.99 Å (-CH_2-), and with $U_{iso}(H) = kU_{eq}(C)$, where k = 1.5 for the methyl groups which were permitted to rotate but not to tilt, and 1.2 for all other H atoms bonded to C atoms. For the H atoms bonded to N atoms, the atomic coordinates were refined, with $U_{iso}(H) = 1.2U_{eq}(N)$, giving the N-H distances shown in Table 3. One low-angle reflection (-1,2,1), which had been attenuated by the beam stop, was omitted from the refinement. In the final analysis of variance there was a large value, 2.838, of K = [mean(F_o^2)/mean(F_c^2)] for the group of 400 very weak reflections having $F_c/F_c(max)$ in the range $0.000 < F_c/F_c(max) < 0.004$: this is probably a statistical artefact.

Table 1. Experimental Details.

Ethyl 4-hydrazinobenzoate hydrochloride	**(E-4HB)**
Crystal data	
Chemical formula	$C_9H_{13}N_2O_2Cl$
M_r	216.66
Crystal system, space group	Triclinic, *P*-1
Temperature (K)	100(2)
a, *b*, *c* (Å)	5.9566 (4), 7.4498 (6), 23.5349 (17)
α, β, γ (°)	84.323 (3), 84.521 (3), 80.257 (3)
V (Å^3)	1020.95 (13)
Z	4
Radiation type	Cu *K*α
μ (mm^{-1})	3.14
Crystal size (mm)	0.12 × 0.10 × 0.04
Data collection	
Diffractometer	*KAPPA* PAEXII DUO
Absorption correction	Multi-scan

	SADABS (Bruker, 2012)
T_{min}, T_{max}	0.668, 0.882
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	16589, 3454, 2562
R_{int}	0.054
$(\sin \theta/\lambda)_{max}$ (Å^{-1})	0.599
Refinement	
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.045, 0.143, 1.10
No. of reflections	3454
No. of parameters	279
H-atom treatment	H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.40, −0.26

2.4. Computational detail.

The accurate representation of Non-Covalent Interactions (NCI) in DFT depends on the choice of the functional/basis set pair. Li et al., studied the interaction energy of molecules from Benchmark Energy and Geometry Database with several functional [24]. The authors found a favorable performance with combination of the M06-2X functional and D3 Grimme's dispersion correction [25]. Similarly, Brauer et al., obtained good results without extra dispersion correction but parameterizing M06-2X for midrange interactions [26]. For the basis sets, Hobza founds the lesser error (as root mean squared error, RMSE) in interaction energy with aug-cc-pVTZ basis set for 66 molecular complexes by using CCSD(T) method [27]. This value was comparable with the complete basis set limit. Rezac and Hobza recommended this basis set in NCI modelling [28]. On these bases, we calculated the electronic structure of these molecules at M06-2X-D3/aug-cc-pVTZ level of theory with Gaussian 09 [29].

All NCI calculations were carried-out with NCIplot 3.0 [30,31], and the isosurfaces graphed with VMD [32]. In this work, we considered three models to evaluate the NCI. The intramolecular interactions were analyzed on the optimized ammonium cation of E-

4HB, named E-4HB+, and E-4HB with the geometry at the unit cell using the density from the wavefunction. The intermolecular interactions were studied with unit cell (UC) using the pro-molecular approach.

3. RESULTS AND DISCUSSION

3.1. Synthesis and spectroscopy characterization of E-4HB.

The compound 4-HBA was synthesized from ethyl *4*-aminobenzoate (**1**) (Scheme 1) as described above (sections 2.2.1 and 2.2.2). Yield = 85%, colourless plates, m.p. = 223-226ºC. FT-IR (KBr, disk) cm^{-1}: 3315.0 (N-H); 1687.6 (C=O); 1600.8 (C=C); 1276.8 (C-O-C). ^{1}H NMR (D_2O, 500 MHz): δ 1.24 (t, 3H, $-CH_3$); 4.24 (c, 2H, $-CH_2-$); 6.63 (d, $2H_{Arom}$, J = 8.7 Hz); 7.91 (d, $2H_{Arom}$, J = 8.9 Hz). ^{13}C NMR (D_2O, 125 MHz): δ 13.5; 62.2; 113.6; 123.8; 131.3; 148.5; 168.6.

3.2. Structure description

Compound (E-4HB) crystallizes in the triclinic space group *P*-1 with two formula units $(C_9H_{13}N_2O_2)^+.Cl^-$ in the asymmetric unit (Figure 1): it will be convenient to refer to the cations containing atoms N11 and N21 as cations of types 1 and 2 respectively. The two aryl rings are nearly parallel with a dihedral angle between them of only $0.54(11)^o$. While the orientations of the two $-NHNH_3^+$ units are very similar, as shown by the relevant torsional angles (Table 2), the orientations of the two EtCOO- units are different. In the type 1 cation, the NH_3^+ unit and the carbonyl O atom adopt a mutually *cis* arrangement, whereas in the type 2 cation, these units adopt a mutually *trans* arrangement, as the torsional angles (Table 2) show. In addition, the ethyl groups adopt different orientations (Figure 1, Table 2): in the type 1 cation, the methyl atom C19 is displaced from the plane of the aryl ring (C11-C16) by only 0.056(7) Å, but the

corresponding displacement in the type 2 cation is 1.546(6) Å. These conformational differences preclude the possibility of any additional crystallographic symmetry. The dihedral angles between the aryl rings and the carboxy groups in the cations of types 1 and 2 are 3.03(11)^{o} and 0.50(12) respectively. The bond distances and interbond angles present no unusual features.

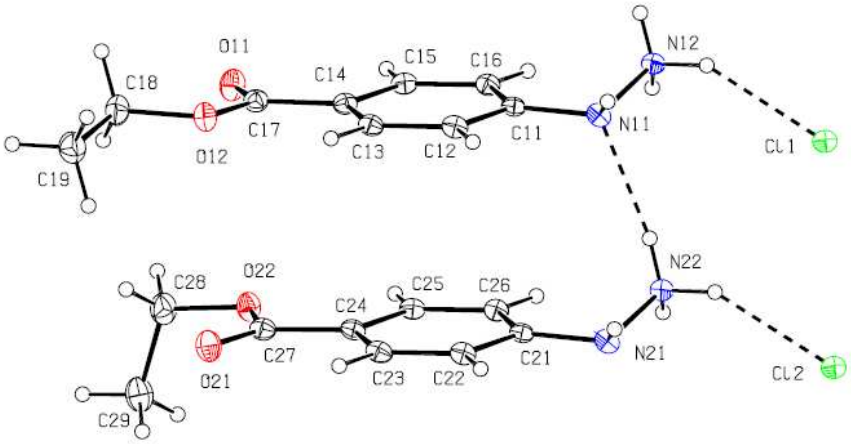


Figure 1. The independent ionic components of compound (E-4HB), showing the atom labelling scheme and the hydrogen bonds (drawn as dashed lines) within the selected asymmetric unit. Displacement ellipsoids are drawn at the 30% probability level.

Table 2. Selected torsional angles (**^{o}**).

Bond Angle	(**^{o}**)	**Bond Angle**	(**^{o}**)
C13-C12-N11-N12	-155.8(2)	C22-C21-N21=N22	-156.4(2)
C13-C14-C17-O11	-177.6(2)	C23-C24-C27-O21	0.9(4)
C13-C14-C17-O12	2.8(3)	C23-C24-C27-O22	-179.8(2)
C14-C17-O12-C18	176.1(2)	C24-C27-O22-C28	176.2(2)
C17-O12-C18-C19	168.4(2)	C27-O22-C28-C29	-82.4(3)

The component ions in compound (E-4BH) are linked by no fewer than ten hydrogen bonds, two of N-H...N type and eight of N-H...Cl type (Table 3). Within the selected asymmetric unit, the ions are linked by one N-H...N hydrogen bond and two N-H...Cl hydrogen bonds to form a four-ion aggregate which can conveniently, although arbitrarily, be regarded as the basic building block of the supramolecular structure. The

seven remaining hydrogen bonds fall into two distinct categories: a second N-H...N hydrogen bond which links aggregates related by translation and six N-H...Cl hydrogen bonds which link aggregates related by inversion.

Table 3. Parameters (Å, ^{o}) for hydrogen bonds.

D-H...A	D-H	H...A	D...A	D-H...A	Symmetry
N11-H11...Cl1	0.80(3)	2.65(3)	3.305(2)	141(3)	1-x,-y,1-z
N11-H11...Cl2	0.80(3)	2.76(3)	3.325(2)	130(3)	1-x,1-y,1-z
N12-H12A...Cl1	0.93(3)	2.29(3)	3.113(2)	148(3)	
N12-H12B...N21	0.85(4)	2.17(4)	3.011(3)	172(3)	x,-1+y,z
N12-H12C...Cl2	0.90(3)	2.38(3)	3.203(2)	152(3)	-x,1-y,1-z
N21-H21...Cl1	0.79(3)	2.75(3)	3.322(2)	131(3)	1-x,1-y,1-z
N21-H21...Cl2	0.79(3)	2.67(3)	3.305(2)	139(3)	1-x,1-y,1-z
N22-H22A...Cl2	0.91(3)	2.30(3)	3.115(2)	149(3)	
N22-H22B...N11	0.86(4)	2.15(4)	3.004(3)	171(3)	
N22-H22C...Cl1	0.88(3)	2.40(3)	3.203(2)	151(3)	-x,1-y,1-z

The two N-H...N hydrogen bonds link aggregates related by translation to form a $C^{2}_{2}(6)$ chain of cations running parallel to the [010] direction, to which the anions are linked by N-H...Cl hydrogen bonds (Figure 2) [33]. The formation of this chain is modestly reinforced by aromatic $\pi\ldots\pi$ stacking interactions. Within the four-ion aggregate, the ring-centroid separation is 3.7224(14) Å and the shortest perpendicular distance from the centroid of one ring to the lane of the other is 3.3006(10) Å, corresponding to a ring slippage of 1.72 Å: For the nearest pairs of ring in adjacent aggregates along the [010] direction, the corresponding distances are 3.3275(14) Å, 3.3096(10) Å and 1.72 Å respectively, leading to a continuous stack of rings along [010] (Figure 3). Chains of this type are linked by the N-H...Cl hydrogen bonds to form a complex sheet lying parallel to (001) (Figure 4).

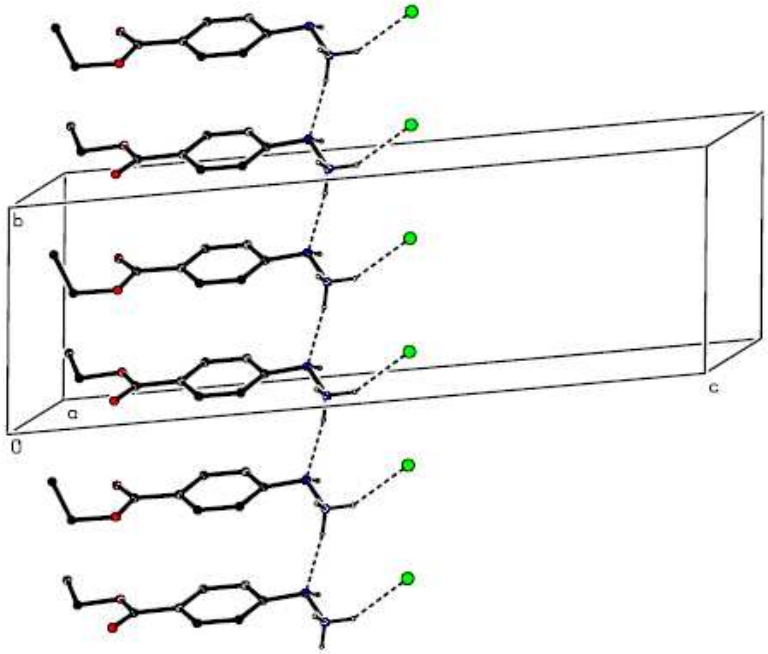


Figure 2. Part of the crystal structure of compound E-4HB showing a hydrogen bonded chain running parallel to the [010] direction and built from aggregates related by translation. For the sake of clarity, the H atoms bonded to C atoms have been omitted.

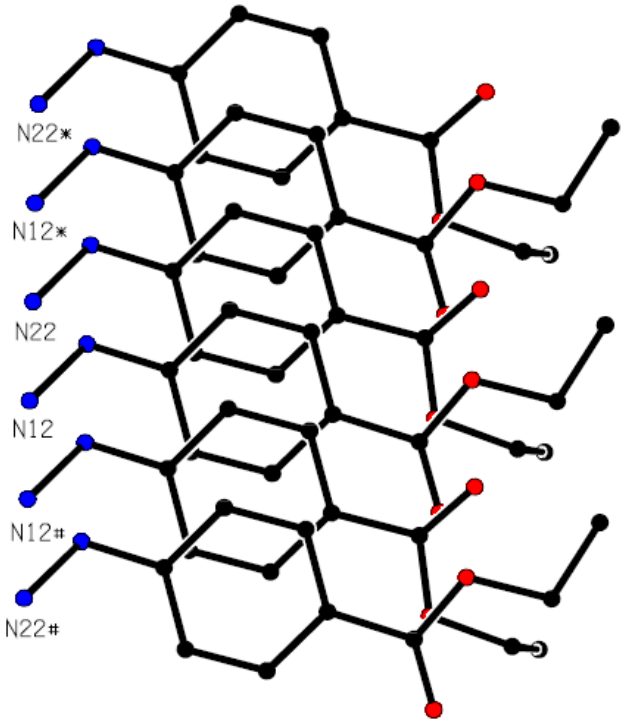


Figure 3. Part of the crystal structure of compound E-4HB showing the aromatic π…π stacking along [101]. For the sake of clarity, the unit-cell outline, the chloride ions, and all of the H atoms have been omitted. The N atoms marked with an asterisk (*) or a hash (#) are at the symmetry positions (x, 1 + y, z) and (x, -1 + y, z) respectively.

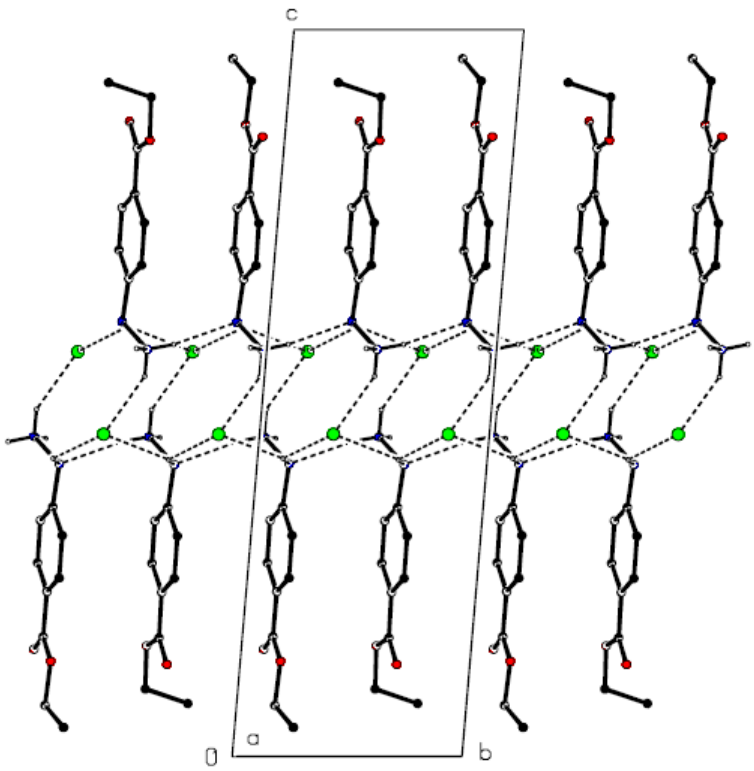


Figure 4. A projection along [100] of part of the crystal structure of compound E-4HB showing the formation of a sheet parallel to (001). For the sake of clarity, the H atoms bonded to C atoms have been omitted.

Each of the chloride ions accepts four N-H...Cl hydrogen bonds (Table 3), and the disposition of the H atoms linked to the Cl ions is very approximately tetrahedral, although significantly distorted from the idealized geometry (Figure 5).

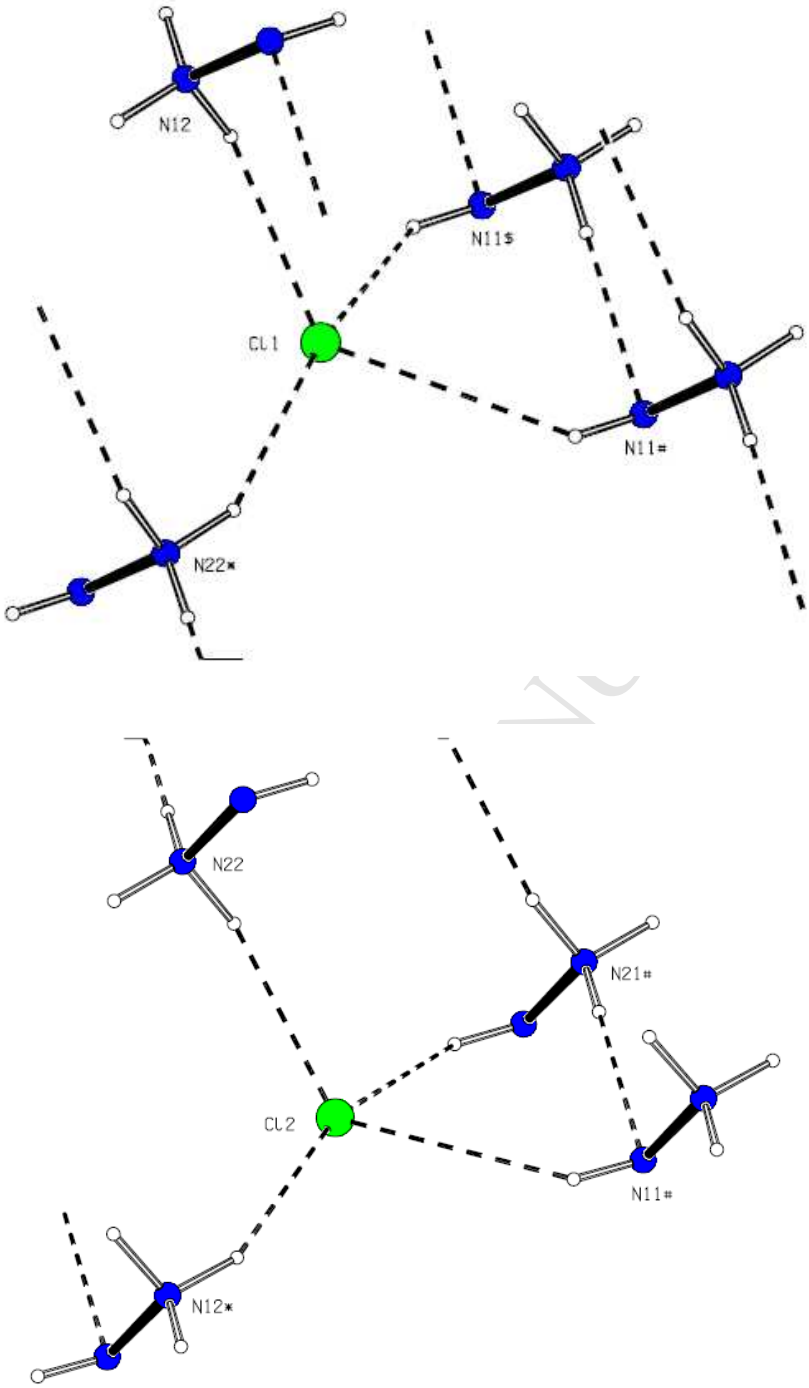


Figure 5. The geometry around each of the independent Cl ions: (a) the hydrogen bonds around Cl1 and (b) the hydrogen bonds around Cl2. For the sake of clarity the ethoxycarbonylphenyl units have been omitted. The N atoms marked with an asterisk (*), a hash (#) or a dollar sign ($) are at the symmetry positions (-x, 1 - y, 1 - z), (1 - x, 1 - y, 1 - z) and (1 - x, -y, 1 - z) respectively.

Finally, we note that while the H...A distances reported in Table 3 are all comfortably within the sums of the van der Waals radii [34], the H...Cl distances associated with the quaternary atoms N12 and N22 are significantly shorter than those associated with the neutral atoms N11 and N21. These two groups of hydrogen bonds show clearly that the shorter group may be regarded as charge-assisted hydrogen bonds [35].

3.2.1. Database survey

The component ions in the unsubstituted analogue of E-4HB, namely phenylhydrazinium chloride, $(PhNHNH_3)^+Cl^-$ are linked by a combination of one N-H...N and three N-H...Cl hydrogen bonds to form simple sheets [16]. In diphenylhydrazinium chloride $(Ph_2NNH_3)^+.Cl^-$, the ions are linked by three N-H...Cl hydrogen bonds to form an elegant chain of edge-fused rings [17], these rings were described in the original report as being of $R^4_2(6)$ type but they are, in fact, of $R^2_4(8)$ type (as, indeed, illustrated in the original report), and two distinct types of such rings, both centrosymmetric, alternate along the chain. Finally we note that 4-ethoxybenzohydrazide, $EtOC_6H_4CONHNH_2$, is an structural isomer of function of neutral Ethyl 4-hydrazinobenzoate, and the molecules are linked into a three dimensional framework structure by a combination of N-H...O, C-H...O and C-H...π(arene) hydrogen bonds [36].

3.3. Non-Covalent Interactions.

In recent years, studies of the reduced gradient of density [s(ρ)] and signed density [sign(λ_2)ρ], commonly known as NCIplot [30,31], have gained popularity for describing the non-covalent interactions in crystals and co-crystals [37,38]. This technique has helped to identify the interactions guiding self-assemblies processes as well as new

types of intermolecular interaction [39,40]. Here we use this technique to explore further the intra and intermolecular non-covalent interactions in the crystals of E-4HB, in the light of the experimentally-determined crystal structure.

The calculated HOMO - LUMO gaps for E-4HB and E-4HB$^+$ are 7.24 and 5.24 eV, respectively. These values are greater than those reported for 2,4-dinitro-, nitro- and phenylhydrazone derivatives of furan-2- and thiophene-2- by Alvarado et al. [41], which lie in the range of 3.1-3.8 eV, at B3LYP/6-311++g(3d,3p) level of theory – See Table 4 [41]. These differences can be attributed to the low electron-withdrawing capacity of the ester moiety and to the lack of conjugation between the phenyl and the NH-NH_3^+ fragment, this lack is clearly shown by the length of the C-N bond, 1.424(3) Å, which is much longer than is found in neutral aniline derivatives, where the mean value is 1.355 Å but closer to that in anilinium salts where the mean value is 1.465 Å [42]. Consequently, E-4HB and E-4HB+ exhibit the behavior of an insulator [43].

Table 4. HOMO and LUMO energies (au) of E-4HB and E-4HB+compared with 2,4-dinitro-, nitro- and phenylhydrazone derivatives of thiophene and furan reported in the literature.

Molecule	**ε_{HOMO} (eV)**	**ε_{LUMO} (eV)**
E-4HB	-12.04	-4.80
E-4HB$^+$	-6.83	-1.54
1-(furan-2-ylmethylene)-2-phenylhydrazine [41]	-5.36	-1.57
1-(thiophen-2-ylmethylene)-2-phenylhydrazine [41]	-5.47	-1.75
1-(furan-2-ylmethylene)-2-(4-nitrophenyl)hydrazine [41]	-6.02	-2.53
1-(thiophen-2-ylmethylene)-2-(4-nitrophenyl)hydrazine [41]	-5.97	-2.56
1-(furan-2-ylmethylene)-2-(2,4-dinitrophenyl)hydrazine [41]	-6.44	-3.16
1-(thiophen-2-ylmethylene)-2-(2,4-dinitrophenyl)hydrazine [41]	-6.42	-3.26

As can be seen from Figure 6, in E-4HB, the HOMO electrons are exclusively on the Cl^- ion, while the LUMO density lies overall structure of the Ethyl 4-Hydrazinium benzoate (E-4HB+). These energies suggest that electron density transfer from counter anion to the Ethyl 4-Hydrazinium benzoate. When the chloride is no present, E-4HB+, the HOMO occupies the backbone of Ethyl 4-Hydrazinium benzoate, and the LUMO is localized predominantly on the Ar-NH-NH_3^+ moiety, phenyl ring and carboxyl group.

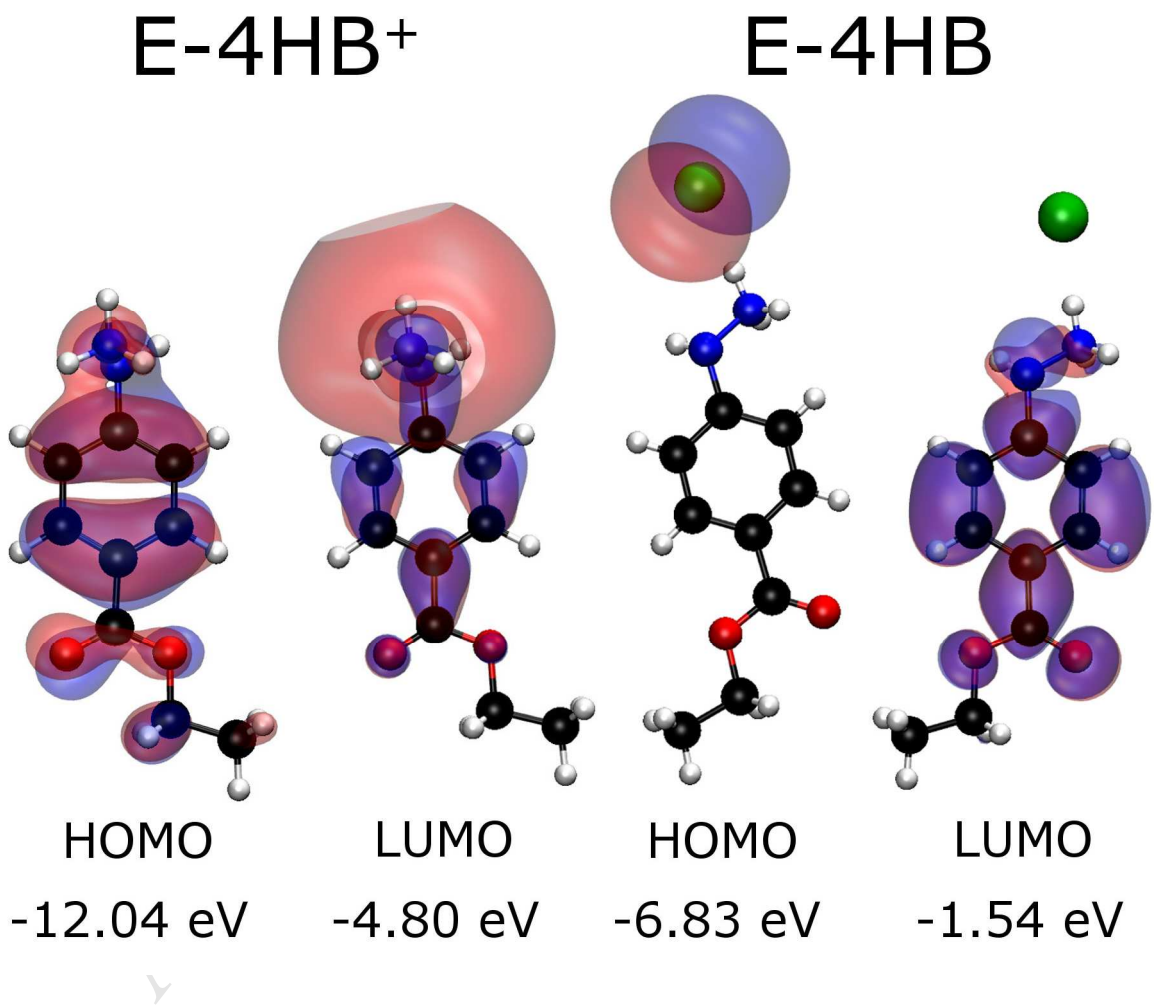


Figure 6. Frontier orbitals of E-4HB+ and E-4HB.

In a NCIplot the non-covalent interactions are identified as the minima of the s(ρ) against sign(λ2)ρ diagram. Their classification in attractive or repulsive is given by the

sign of the second eigenvalue (λ_2) of the density hessian matrix. The value of ρ is related to the strength of interaction. Then, the NCI are visualized by a color-coded reduced density gradient isosurface.

The NCIplots reveal the common intramolecular interactions, i.e. ring clash, repulsive and attractive van der Waals interactions (Figure 7). The value of the signed density [sign(λ_2)ρ] ca. 0.025 au with reduced density gradient (s) going to zero in the bottom left of the figure suggest a strong electrostatic interaction between chloride and the amino nitrogen. It is accepted that the relative strength of the hydrogen bond is related to the difference between the attractive ($\lambda_2 < 0$) and repulsive ($\lambda_2 > 0$) parts of the integral of density over the NCI domain [44]. This technique has revealed, by an analysis of sign(λ_2)ρ, the preference of the six-membered ring conformation over the five-membered ring conformation in intramolecular hydrogen bonded α- and β-D-glucose [45]. In crystals, the techniques have been capable to characterize the different strength of hydrogen bonds in urea crystals [46].

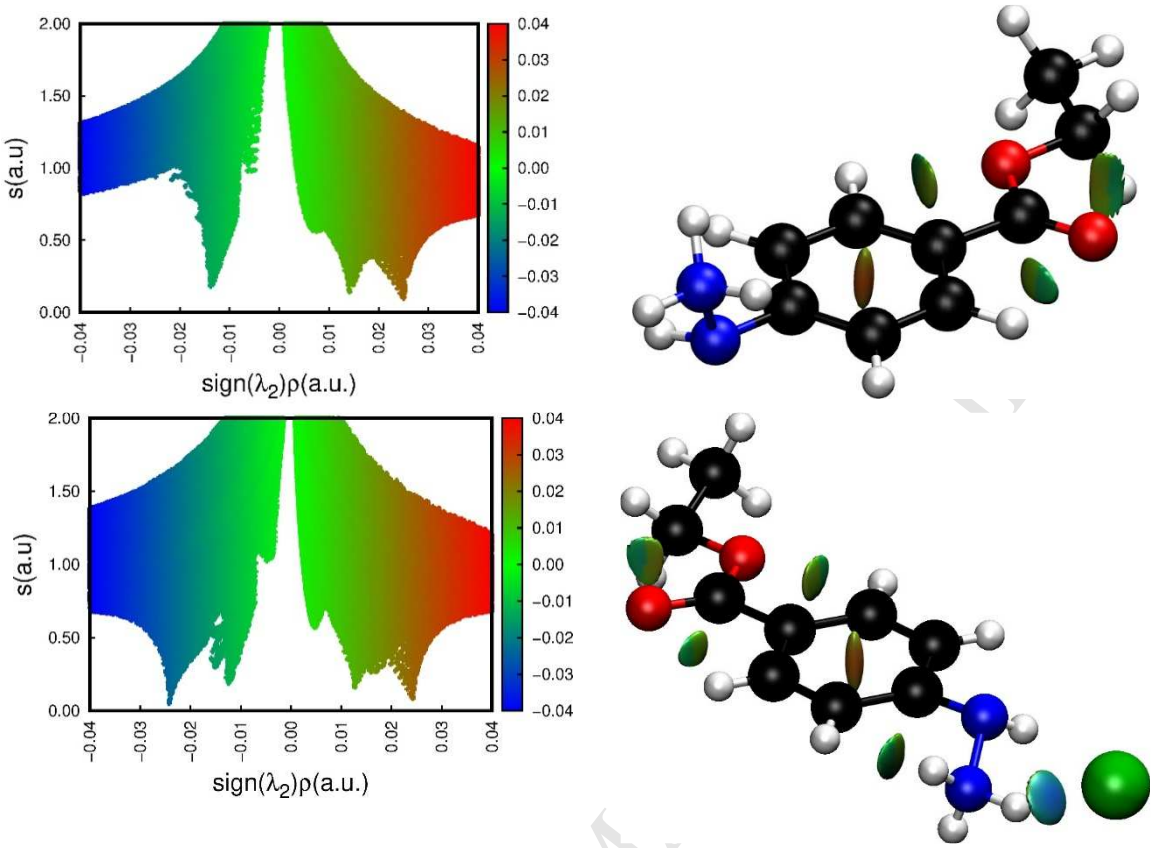


Figure 7. NCIPlot of E-4HB^{+} (top) and E-4HB (bottom)

The pro-molecular NCIplot supports the crystallographic findings concerning the intermolecular hydrogen bonds. Figure 8 shows the strong hydrogen bond N-H...N located between sign(λ_2)ρ of -0.035 and -0.025 au. According to Contreras-García the binding energy is related to the difference between the attractive ($\lambda_2 < 0$) and repulsive ($\lambda_2 > 0$) parts of the integral of density over the NCI domain [24] Consequently, in the unit cell, this is the strongest interaction, since there is no repulsive counterpart.

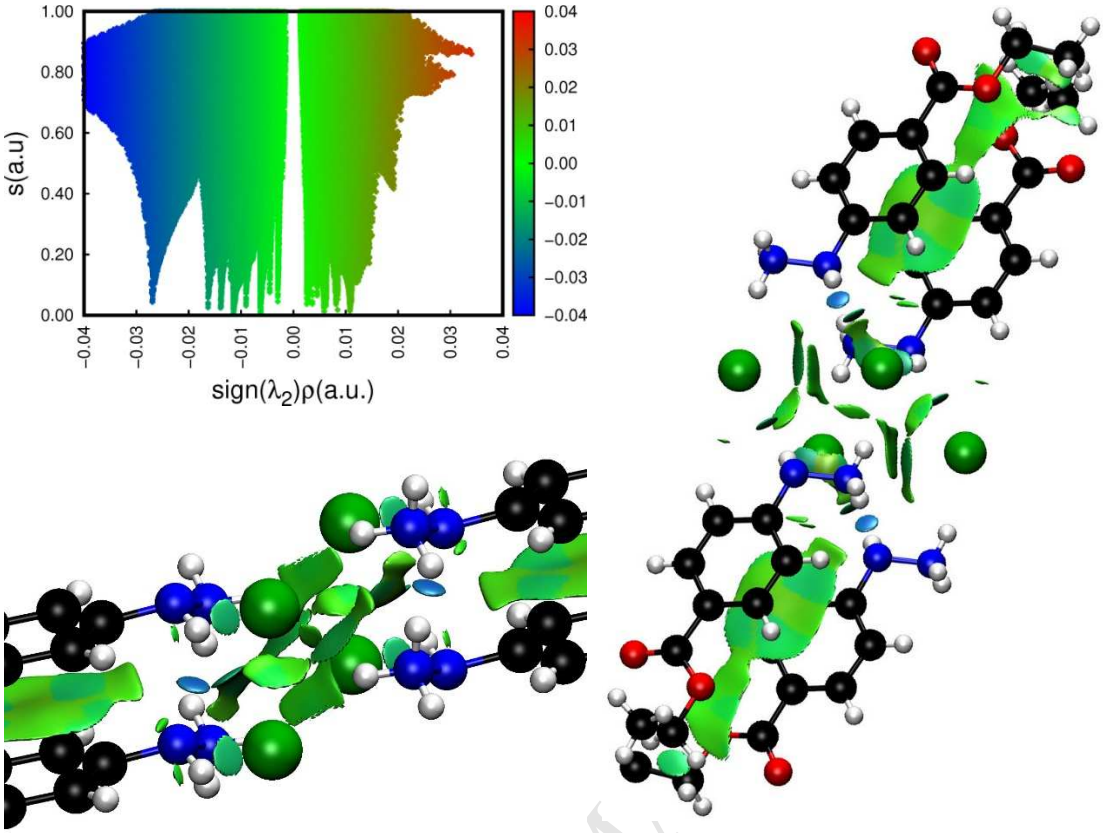


Figure 8. NCIPlot of unit cell of E-4HB. The top-bottom figure is a zoom of the -NH-NH_3^+ ...Cl^- region.

Another type of hydrogen bond in the molecule is observed between -0.013 and -0.020 au. In this case, the secondary amine hydrogen bonds chloride anion. This bond is weakened by steric repulsions and the distribution of these Cl^-...H-N bonds across several NH moieties [25]. Finally, the attractive Coulombic interaction C=NH-NH_3^+… Cl^- at 0.025 au in bottom left of the Figure 7 is observed below -0.01 au in the Figure 8. Finally, the Coulombic repulsion between π-rings in a phenyl dimer leads to a parallel-displaced structure [26].

4. CONCLUSIONS

The structural analysis of ethyl 4-hydrazinobenzoate hydrochloride (E-4HB), $C_9H_{13}N_2O_2Cl$, has been established by single crystal X-ray diffraction, and this is the

first X-ray report of this compound. The component ions are linked by ten hydrogen bonds, two of N-H···N type and eight of N-H···Cl type. The NCIplot supports the crystallographic observations and allows estimation of the relative strength of N-H···N and N-H···Cl interactions.

5. SUPPLEMENTARY MATERIAL

X-ray crystallographic data for this structure has been deposited at the Cambridge Crystallographic Data Center under code CCDC 1563976. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/structures/, or from the e-mail deposit@ccdc.cam.ac.uk.

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Highlights

In this article we can highlight the following:

- The synthesized compound is an intermediate for the synthesis of new compounds with pharmacological interest.

- There is little evidence in the literature on this type of derivatives and the first report is more than 50 years old.

- The crystallographic data reveal that compound 4-EHB forms complex sheets stabilized by hydrogen bonds of type N-H...N and N-H...Cl, forming two and eight bonds respectively.

- The crystallographic observations were confirmed through the results obtained with the non-covalent interactions calculations, which also allow to make estimations about the intensity of the interactions N-H…N and N-H…Cl.